METHAMIDOPHOS

REVISED TOXICOLOGY CHAPTER FOR RED

DP Barcode No.:	D256737	Submission No.:	S559490
Rereg. Case No.:	819351	P.C.Code No.:	101201
CAS Registry No.	10265-92-6	Tox. Chem. No.	378A
Composition:	O,S-Dimethyl phosphoramidothioate		
Chemical Class:	Organophosphorus pesticides		

Prepared by: Nancy E. McCarroll, Toxicology Branch 1/HED Date:

Reviewed by: Alberto Protzel, Ph.D. Branch Senior Scientist Toxicology Branch 1/HED Date:

Human Health Assessment

1. Toxicology Assessment

The toxicology profile for Methamidophos is summarized in Table 1. The toxicology database is complete and is adequate to support the reregistration eligibility of methamidophos as a food use pesticide.

Table 1. Toxicology Profile for Methamidophos (Monitor)

GUIDELINE NO.	TYPE OF STUDY	MRID NO(s)	REQUIRED	SATISFIED
81-1	Acute Oral	00014044	Yes	Yes
81-2	Acute Dermal	00014049	Yes	Yes
81-3	Acute Inhalation	00148449	Yes	Yes
81-4	Primary Eye	00014221	Yes	Yes
81-5	Primary Dermal	00014220	Yes	Yes
81-6	Dermal Sensitization	00147929	Yes	Yes
81-7	Acute Delayed Neurotoxicity/Hen	00041317	Yes	Yes
81-8	Acute Neurotoxicity/Rat	43025001; 43345801	Yes	Yes
82-1(a)	90-Day Oral Toxicity/Rat	00014155	Yes	No[a]
82-1(b)	90-Day Oral Toxicity/Dog	00014153	Yes	No[a]
82-1SS	8-Week Subchronic Oral Toxicity Cholinesterase Study/Rat	41867201	No	Yes
82-1SS	Subchronic Oral Cholinesterase Study/Human	00015160	No	NA
82-2	21-Day Dermal Toxicity	44525301	Yes	Yes
82-4	90-Day Inhalation Toxicity	41402401	Yes	Yes
82-5(a)	90-Day Delayed Neurotoxicity/Hens	40985202	Yes	Yes
82-5(b)	90-Day Neurotoxicity/Rat	43197901	Yes	Yes
83-1(a)/83-2(a)	Combined Chronic Toxicity/Carcinogenicity/Rat	00148952	Yes	Yes
83-1(b)	Chronic Toxicity/Dog	00147938	Yes	Yes
83-2(b)	Carcinogenicity/Mouse	00145579	Yes	Yes
83-3(a)	Developmental Toxicity/Rat	00148454; 43906901	Yes	Yes

Table 1. Toxicology Profile for Methamidophos (Monitor)

GUIDELINE NO.	TYPE OF STUDY	MRID NO(s)	REQUIRED	SATISFIED

83-3(b)	Developmental Toxicity/Rabbit	00041315; 44040601	Yes	Yes
83-4	2-Generation Reproduction Toxicity	00148455/ 41234301	Yes	Yes
84-2	Mutagenicity/Gene Mutation (Bacteria)	00098457	Yes	Yes
84-2	Mutagenicity/Gene Mutation (Mammalian Cells)	42854701	Yes	Yes
84-2	Mutagenicity/Chromosome Aberrations (In vitro)	41461401	Yes	Yes
84-2	Mutagenicity/Chromosome Aberrations (In vivo)	41234306	Yes	Yes
84-2	Mutagenicity/Other Mutagenic Mechanisms (In vitro)	41234305	Yes	Yes
85-1	Metabolism Study	00015224	Yes	Yes[b]

[a] Requirement satisfied by MRID No. 41867201.
[b] MRID No. to be assigned; review of study is pending.
[b] Study is classified acceptable nonguideline and does not satisfy the current guideline requirement but the available data do allow the basic characterization of the metabolism of Methamidophos.

a. Acute Toxicity

Table 2 presented below summarizes the acute toxicity studies with Methamidophos and the toxicity categories for the different routes of administration.

Table 2. Acute Toxicity of Methamidophos

Guideline No.	Study Type	MRIDs #	Results	Toxicity Category
81-1	Acute Oral; Rat 95.0% a.i.	00014044	LD_{50} = 15.6 mg/kg ♂ LD_{50} = 13.0 mg/kg ♀	I
81-2	Acute Dermal; Rabbit 75% a.i.	00014049	LD_{50} = 118 mg/kg ♂	I
81-3	Acute Inhalation; Rat 70.5% a.i.	00148449	LC_{50} = 0.052-0.079 mg/L[a] ♂ LC_{50} = 0.062-0.128 mg/L[a] ♀	I
81-4	Primary Eye Irritation; Rabbit 72.3% a.i.; dose: 0.1 mL	00014221	Corneal opacity and pannus present in 2/6 rabbits for 10 days posttreatment. One death 30 min. after dosing	I
81-5	Primary Skin Irritation; Rabbit 73% a.i. dose: 0.1 mL	00014220	PIS = 0.6 but test material was lethal to 5/9 animals within 24 hrs. of treatment	I
81-6	Dermal Sensitization; Guinea Pig 73.8% a.i.	00147929	Not a skin sensitizer (modified Buehler test)	--

[a] 95% Confidence limit

As shown, Methamidophos is acutely toxic, causing death shortly after exposure to relatively low oral (LD_{50} = 15.6 mg/kg ♂; 13.0 mg/kg ♀), dermal (LD_{50} = 118 mg/kg/day ♂) or inhalation doses (LC_{50} = 0.063 mg/L ♂; 0.076 mg/L ♀). Methamidophos is only moderately irritating to the eyes and only mildly irritating to the skin. However, deaths and other signs of systemic toxicity occurred shortly after dermal or ocular application. These findings suggest that Methamidophos is rapidly absorbed via these routes. Other toxic signs observed in animals treated acutely with Methamidophos are consistent with cholinesterase inhibition and are typical of the acute toxic signs induced by the organophosphate class of chemicals. They included: tremors, salivation, chromodacryorrhea (bloody tears) and dyspnea (labored breathing).

Summarized findings from the above acute toxicity studies were as follows:

In an acute oral toxicity study, deaths within 20 minutes to 72 hours of the administration of *Methamidophos (95% a.i.)* occurred as follows: all male and female Sprague Dawley rats receiving 25.4 mg/kg, 80% at 17.0 mg/kg, 50% at 14.2 mg/kg and 20% at 11.3 mg/kg;

no deaths occurred in the lower treatment groups (5.0 or 7.5 mg/kg). Signs of toxicity (evident within 5-10 minutes) included severe tremors, salivation, chromodacryorrhea, dyspnea, rhinorrhea and rarely, clonic convulsions. All survivors recovered within 7 days and no pathological changes were noted in survivors 14 days postdosing.

This acute oral study is classified acceptable; it satisfies the guideline requirement for an acute oral study (81-1) in the rat (MRID No. 00014044).

In an acute dermal toxicity study, deaths generally within 6-48 hours of treatment with *Methamidophos (75% a.i.)* occurred as follows: one New Zealand White rabbit died at 100 mg/kg (lowest dose tested) and all rabbits receiving either 156 or 222 mg/kg died; the majority of deaths occurred within 6-48 hours. Signs of toxicity (evident within 1-3 hours) included severe miosis, salivation, rhinorrhea, ataxia, and apparent CNS depression. All survivors recovered completely within 14 days and no pathological changes were noted in survivors 14 days postdosing.

This acute dermal study is classified as acceptable; it satisfies the guideline requirement for an acute dermal study (81-2) in the rabbit (MRID No. 00014049).

In an acute inhalation toxicity study, mortality of Sprague Dawley rats (within 0-2 days ♂; 0-5 days ♀) occurred as follows: all ♀ receiving 0.173 mg/L; 80% of ♂ and 50% of ♀ receiving 0.082 mg/mL; 60% ♀ at 0.62 mg/L; 40% ♂ and 40% ♀ at ≈0.057 mg/L and 10% ♂ at 0.033 mg/L *Methamidophos (70.5% a.i.)*. Rats of both sexes in all treatment groups (0.019-0.173 mg/L) showed toxic signs which included: salivation, lacrimation, muscle fasciculations, tremors, decreased activity, piloerection and hypothermia. Ocular and nasal irritation and occasional corneal opacity were also observed. Clinical signs lasted for 1-10 days (♂) or 1-14 days (♀). Significant body weight reductions were recorded for all dosing groups on days 3 and 7 (♂) and day 3 (♀). Dark or red lungs were also reported for the treated animals.

This acute inhalation study is classified as acceptable; it satisfies the guideline requirement for an acute inhalation study (81-3) in the rat (MRID No. 00148449).

In a primary eye irritation study, one New Zealand White rabbits with **unwashed eyes** died 30 minutes post-treatment with 0.1 mL of *Monitor technical (72.0-76.0% Methamidophos)*. Toxic signs (tremors, salivation, diarrhea and miosis) were apparent in all

rabbits until 1 day postdosing. These data suggest that Methamidophos was readily absorbed from the conjunctival sac of the eye into the blood stream. Corneal opacity and conjunctivitis were seen through 72 hours and iritis was noted up to 24 hours. Corneal opacity and pannus persisted in two rabbits for 10 days postexposure.

This study is classified as acceptable; it satisfies the guideline requirement for a primary eye irritation study (81-4) in the rabbit (MRID No. 00014221).

In a primary dermal irritation study, five of nine New Zealand White rabbits died within 24 hours of treatment with 0.1 mL of *Monitor Technical (73% Methamidophos)* delivered to one intact and one abraded area of the skin. Toxic signs observed shortly after application included: ataxia, increased respiration, salivation, miosis, tremors, diarrhea and collapse. At 24 hours, the four surviving rabbits had well-defined erythema and 2/4 had slight edema. No erythema or edema was seen at 96 hours. Based on the dermal reaction, the PIS = 0.6.

This study is classified as acceptable; it satisfies the guideline requirement for a primary dermal irritation study (81-5) in the rabbit (MRID No. 00014220).

In a dermal sensitization study, a 25% solution of SX-1490 *(73.8% Methamidophos)* prepared in distilled water was not a sensitizing agent to Hartley albino guinea pigs under the conditions of the modified method of Buehler. The positive control, 1-chloro-2,4-dinitrobenzene induced the expected dermal sensitization response.

This study is classified as acceptable; it satisfied the guideline requirement for a dermal sensitization study (81-6) in the guinea pig (MRID No. 00147929).

b.1 Subchronic Toxicity

Sufficient data are available on the subchronic toxicity of Methamidophos. The most consistent toxicological findings associated with exposure to Methamidophos were decreased body weight gain (rats) and inhibition of plasma, erythrocyte and/or brain cholinesterase (hens, rats, dogs and humans). Regardless of the route of exposure (oral, dermal or inhalation), cholinesterase (ChE) inhibition was consistently detected from the initial sampling time (generally 1 week) to study termination. In

general, the magnitude of the response did not increase with time.

Summarized findings supporting the above conclusions from the subchronic toxicity studies are presented below:

Subchronic oral rat study

In a subchronic toxicity study, *BAY 71628 technical (70% Methamidophos)* was administered to 15 male and 15 female Wistar rats/dose in the diet at 2, 6, 20 or 60 ppm (equivalent to 0.1, 0.3, 1.0 or 3.0 mg/kg/day). Treatment with BAY 71628 had no effect on mortality, hematology, clinical chemistry, urinalysis or gross necropsy. At 60 ppm, male rat body weight gain was significantly reduced and food consumption was also decreased. Rats at 60 ppm were quiet and appeared weak; however, cholinergic signs were not observed in either sex. The only effect observed in the females occurred in the high-dose (i.e., significantly decreased thymus weights).

The systemic LOEL is 60 ppm (3 mg/kg/day) based on significantly decreased male body weight gain and decreased food consumption and clinical signs in both sexes. The NOEL is 20 ppm (1.0 mg/kg).

Cholinesterase (ChE) activity in plasma and erythrocytes was determined at weeks 1, 4, 8 and 13; brain ChE was not determined. Inhibition of plasma and erythrocyte ChE was dose related at all sampling times; however, a clear time-dependent response was not seen. Inhibition after 13 weeks of treatment with 60 ppm was 55-71% (plasma--both sexes) or 71-76% (RBC--both sexes). Also after 13 weeks exposure to 6 ppm, ChE inhibition was 15-25% (plasma--both sexes) or 14-24% (RBC--both sexes). ChE inhibition for both sexes at the 2-ppm level ranged (over 13 weeks) from 0 to 11% (plasma) or from 0 to 14% (RBC).

The ChE LOEL = 6 ppm (0.3 mg/kg/day), based on plasma and RBC ChE inhibition in both sexes. The NOEL is 2 ppm (0.1 mg/kg/day).

This subchronic toxicity study is classified supplementary because brain ChE determination and histopathology were not performed. It does not satisfy the guideline requirement for a subchronic oral study (82-1a) in rats (MRID No. 00014155).

Subchronic oral dog study

In a subchronic toxicity study, *BAY 71628 technical (70% Methamidophos)* was administered to 2 male and 2 female Beagle

dogs/dose in the diet at dose levels of 1.5, 5 or 15 ppm (equivalent to ≈0.0375, 0.125 or 0.375 mg/kg/day). Treatment with BAY 71628 had no effect on appearance, behavior, mortality, food intake, body weight, hematology, clinical chemistry, urinalysis, organ weight or gross necropsy; histopathology was not performed.

A LOEL for systemic effects was not established. The NOEL is 15 ppm (0.375 mg/kg/day).

Cholinesterase (ChE) activity in plasma and RBCs was determined at week 1 and at 1, 2 and 3 months; brain ChE was not determined. Inhibition of plasma and RBC ChE, which was initially observed at week 1, was dose related. In general, ChE inhibition peaked at 2 months but persisted to study termination; the response was generally more pronounced in females. At the 1.5 ppm level, inhibition of plasma and RBC ChE for both sexes ranged from 0-16% or from 0-20%, respectively. At 5 ppm, inhibition of plasma and RBC ChE for both sexes ranged from 6-38% or 7-42%, respectively. At the high dose (15 ppm), inhibition of plasma and RBC ChE for both sexes ranged from 17-61% and 37-81%, respectively.

THE ChE LOEL is 5 ppm (0.125 mg/kg/day), based on plasma and RBC ChE inhibition in both sexes. The NOEL is 1.5 ppm (0.0375 mg/kg/day).

This subchronic toxicity study is classified supplementary because an insufficient number of animals/group were evaluated, and brain ChE determinations and histopathology were not performed. It does not satisfy the guideline requirement for a subchronic oral study (82-1b) in dogs (MRID No. 00014153).

Subchronic dermal rat study

In a 21-day dermal toxicity study, Methamidophos Technical (76.9 to 80.5% a.i.)] was administered to 9 to 10 male and female Sprague-Dawley rats dermally in pH 7.3 phosphate buffer solution (dose volume of 1 ml/kg of body weight) at dose levels of 0, 1, 15, and 50 mg/kg/day.

Since the Technical material has a relatively low concentration of active ingredient, dose levels corrected in terms of active ingredient are significantly lower. The corrected dose levels would then be 0.749, 11.2, and 36.5 mg/kg/day (using the actual analytically confirmed values of 0.974, 14.5 and 47.4 mg/kg/day, respectively and 76.9% a.i). These dose levels should be utilized for risk assessment purposes.

No compound related effects on mortality, clinical signs, body weight, food consumption, or gross and histopathology were apparent at any dose level. Dose related plasma, RBC and brain cholinesterase inhibition were noted at 15 and 50 mg/kg/day of technical. A statistically significant increase in relative lung weights was observed at the high dose males, but this was not supported by histopathologic findings. Therefore, the **LOEL is 11.2 mg/kg/day technical (based on correction of the nominal, 15 mg/kg/day, for the analytical concentration of the active ingredient)and is based on brain, RBC and plasma cholinesterase inhibition. The NOEL is 0.749 mg/kg/day technical (based on correction of the nominal, 1 mg/kg/day, for the analytical concentration of the active ingredient).**

This dermal toxicity study was originally classified as unacceptable due to the lack of analytical and stability data. Based upon the addendum report submitted on September 29, 1998, this study is upgraded to acceptable and now satisfies the guideline requirement for a 21-day dermal study (82-2) in the rat (MRID No. 44525301 and Addendum to MRID No. 44525301).

Subchronic inhalation rat study

In a subchronic inhalation toxicity study, Wistar rats, 10/sex/dose, were exposed to an aerosol of SRA 5172 *(Methamidophos, 73.4%)* for 3 months (head/nose only, 6 hours/day, 5 days/week).

The mean analytical concentrations of SRA 5172 in the exposure chambers were 0 (air control), 0 (vehicle control), 1.1, 5.4 and 23.1 mg/m^3 or 0, 0, 0.0011, 0.0054 and 0.0231 mg/L, respectively. Polyethylene glycol E 400:ethanol (1:1) was the vehicle in which SRA 5172 was aerosolized. The mean mass median aerodynamic diameters (MMAD) of the SRA 5172 particles in the exposure chambers for the low-dose, mid-dose and high-dose groups were 1.52 ± 0.13, 1.26 ± 0.04 and 1.53 ± 0.09 um, respectively.

Treatment-related effects were not observed in the low-dose group. Relative to the vehicle control values, the only effect observed in the mid-dose male and female was the inhibition of cholinesterase (ChE) activities in erythrocytes (7-28%; $p<0.05$ or 0.01) and plasma (38-63%; $p<0.05$ or 0.01) throughout the treatment period and brain (25-29%; $p<0.01$) at the end of the study. There was no substantive difference in the magnitude of the response on plasma or erythrocyte ChE inhibition from weeks 1-13.

The following effects were observed in the high-dose male and female rats when compared with the vehicle control rats: **(1)** slight to moderate muscle tremors and aggressive behavior; **(2)** decreased

body weight gain (53%); **(3)** decreased food consumption (5-28%); **(4)** increased plasma lactate dehydrogenase (63%) and glutamate oxaloacetate transaminase (32%) activities in males only; **(5)** decreased plasma protein (8%), cholesterol (16-19%) and glucose concentrations (10-11%); **(6)** inhibition of ChE activities in erythrocytes (15-44%; P<0.05 or 0.01) and plasma (53-93%; P<0.01) throughout the treatment period and brain (45-47%) at study termination; there was no substantive difference in the magnitude of the response on plasma or erythrocyte ChE inhibition from weeks 1-13 and **(7)** decreased spleen weight, both absolute (15-25%; P<0.01) and relative (organ/body weight ratio, 11%; P<0.01). When treatment was discontinued, ChE activities in the erythrocytes and plasma (not determined in the brain) returned to the pretreatment values.

The systemic LOEL for both sexes is 23.1 mg/m^3 (0.0231 mg/L), based on clinical signs, decreased body weight gain and feed consumption, altered clinical chemistry parameters, and decreased spleen weights. **The NOEL is 5.4 mg/m^3 (0.005 mg/L).**

Based on the inhibition of ChE activities in erythrocytes, plasma and brain, **the NOEL and LOEL for both sexes are 1.1 mg/m^3 (0.001 mg/L) and 5.4 mg/m^3 (0.005 mg/L),** respectively.

This study is classified as acceptable and satisfies the requirement, 82-4, for a subchronic inhalation toxicity study in the rat (MRID No. 41402401).

b.2 Special Subchronic Toxicity Studies (Cholinesterase Inhibition)

Subchronic oral rat study

The objective of this study was to establish a NOEL for the Methamidophos-induced cholinesterase (ChE) inhibition in plasma, erythrocytes (RBCs) and brain of the rat.

Technical Methamidophos (77.6% a.i.) was administered in the feed to Fischer 344 rats (25/dose/sex) for 56 days at nominal concentrations of 0 (not detected), 0.5, 1, 2 and 4 ppm (analytical concentrations were 0, 0.49, 0.97, 2.12 and 4.30 ppm, respectively), expressed as active ingredient. Based on daily consumption of Methamidophos, these concentrations were equivalent to 0, 0.03, 0.07, 0.13 and 0.24 mg/kg/day, respectively, for the males and 0, 0.06, 0.06, 0.17 and 0.28 mg/kg/day, respectively, for the females. Plasma and RBC ChE activities were determined on study days 14, 28, 42 and 51, and brain ChE activity was determined on study days 14, 35 and 56.

Methamidophos had no effect on body weight gain or food consumption of both sexes. There were no mortalities, and toxic signs usually associated with ChE inhibition were not observed. The only systemic effect, which was seen at all dose levels and all sampling intervals, was the inhibition of ChE activities in the plasma, RBCs and brain.

The inhibition of acetyl and butyryl ChE activity in plasma, and acetyl ChE activity in RBC and brain at 0.5 ppm (0.03 mg/kg/day), for both sexes was considered by the Reference Dose (RfD)/Peer Review Committee on May 29,1992 to define the threshold LOEL for this chemical. Subsequently, the Health Effects Division (HED) Hazard Identification Science Assessment Review Committee (SARC) revaluated the study on January 20, 1998 and determined that 0.5 ppm (0.03 mg/kg/day) is a NOEL. The basis for this decision includes: the magnitude of ChE inhibition in the brain at 0.03 mg/kg/day is small (3-5% ♂ and 0-5% ♀); only reached statistical significance at day 56 (3%) in ♂ and at day 35 (5%) in ♀; and appeared to be within or close to the detection level of this assay. Consequently, the LOEL and NOEL for this study have been determined to be 0.06 mg/kg/day and 0.03 mg/kg/day, respectively, for both sexes.

This subchronic toxicity study is classified acceptable and satisfies the guideline requirement for a subchronic oral study (82-1 Special Study) in rats (MRID No. 41867201).

Subchronic oral human study

In a subchronic study in humans, seven male and seven female volunteers were given mixtures of *Methamidophos (Monitor; purity not stated)* and Acephate (Orthene) in two ratios, 1:4 or 1:9 (Monitor:Acephate) in gelatin capsules containing corn oil. The group receiving the 1:9 ratio (3 males and 3 females) were given 0.1, 0.2, 0.3 or 0.4 mg/kg/day of the mixture (equivalent to 0.01, 0.02, 0.03 or 0.04 mg/kg/day Methamidophos). The group receiving the 1:4 ratio (2 males and 2 females) was given only 0.1 or 0.2 mg/kg/day (equivalent to 0.02 or 0.04 mg/kg/day Methamidophos). Each group received increasing levels of the test materials until a significant inhibition of ChE activity occurred (i.e., ChE inhibition "was greater than two standard deviations below mean pretest activity for two consecutive bleedings"). Dosing human subjects with graded levels of Monitor:Orthene mixtures for a total of 37-73 days had no effects on RBC ChE activity, hematology, blood chemistry, blood pressure, pulse rate, pupil size, light reflex, eye accommodation, chest sound, muscle tone, knee jerk, tongue tremor or finger tremor. The only systemic effect was the significant inhibition of plasma ChE activities in the 1:4 and 1:9

(Monitor:Orthene) groups. In the 1:4 group, significant inhibition was first noted at 0.2 mg/kg/day; it occurred after 16 days and in all subjects. Significant plasma ChE inhibition was first detected in the 1:9 group at 0.3 mg/kg/day level after 21 days of dosing but only in the male subjects. The first significant response observed in the 1:9 group females occurred at 0.4 mg/kg/day level after 10 days of dosing (2 of the 3 females exhibited significant ChE depression). All suppressed ChE activity returned to the pretest values during the 7-day recovery period.

Based on the findings, NOELs and LOELs were as follows:
1:4 mixture: NOEL (both sexes) = 0.1 mg/kg/day (≈0.02 mg/kg Methamidophos); LOEL = 0.2 mg/kg/day (≈0.04 mg/kg Methamidophos)
1:9 mixture: NOEL (♂) = 0.2 mg/kg/day (≈0.02 mg/kg Methamidophos); LOEL = 0.3 mg/kg/day (≈0.03 mg/kg Methamidophos)
1:9 mixture: NOEL (♀) = 0.3 mg/kg/day (≈0.03 mg/kg Methamidophos); LOEL = 0.4 mg/kg/day (≈0.04 mg/kg Methamidophos)

This subchronic toxicity study in humans was classified acceptable as supplementary data. However, at the January 20, 1998 HED Hazard Identification Assessment Review Committee (HIARC) meeting, it was concluded after careful re-evaluation of all appropriate data, that the human data were not considered adequate(see HED Document No. 012477) Therefore, this subchronic toxicity study in humans is classified as unacceptable (MRID No. 00015160).

c. Chronic Toxicity

Sufficient data are available to assess the chronic toxicity and carcinogenic potential of Methamidophos. In agreement with the data from subchronic studies, the most consistent toxicological findings following chronic Methamidophos exposure were decreased body weight gain (rats and mice) and inhibition of plasma, erythrocyte and/or brain cholinesterase (rats and dogs). In addition, Methamidophos has been classified in **"Group E"** (i.e., the chemical is characterized as **"Not Likely"** to be carcinogenic in humans via relevant routes of exposure) because there is no evidence that Methamidophos altered the spontaneous tumor profile in rats or mice.

Summarized findings supporting the above conclusions from the chronic toxicity studies are presented below:

Chronic dog study

In a one-year chronic toxicity study, *Methamidophos technical (70% a.i.)* was administered to 6 Beagle dogs/sex/dose in the diet at dose levels of 0, 2, 8 or 32 ppm (equivalent to 0, 0.05, 0.2 or

0.8 mg/kg/day). There were no significant effects on mortality, clinical signs, body weights, food consumption, hematology, clinical chemistry, urinalysis, organ weights, or gross and histologic pathology.

The systemic NOEL is >32 ppm (>0.8 mg/kg/day).

The cholinesterase (ChE) data indicate that inhibition of brain, plasma and RBC ChE was dose related in both sexes and occurred at all doses throughout the study. At the highest dose tested (32 ppm), brain ChE was inhibited 66-71%, plasma ChE inhibition ranged from 39-66% of control and RBC ChE ranged from 70-84% of control. At the lowest dose tested (2 ppm), brain ChE was inhibited 11-18%, plasma ChE was suppressed 6-23% and RBC ChE activity was inhibited 0-19%.

The ChE LOEL is 2 ppm (≈0.05 mg/kg/day, lowest dose tested), based on brain, plasma and erythrocyte ChE inhibition. A NOEL was not established for ChE inhibition.

This chronic study in the dog is acceptable and satisfies the guideline requirement for a one-year feeding chronic study (83-1) in the dog (MRID Nos. 00147938 [main study]/41234304 [additional data]).

Combined chronic/carcinogenicity rat study

In a chronic/carcinogenicity toxicity study, *Methamidophos technical (70.0-71.5% a.i.)* was administered to 50 Fischer 344 rats/sex/dose in the diet at dose levels of 0, 2, 6, 18 or 54 ppm (equivalent to 0, 0.1, 0.3, 0.9 or 2.7 mg/kg/day) for 106 weeks. There were no significant effects on mortality, food consumption, hematology, clinical chemistry, organ weights, or gross and histologic pathology (urinalysis was not performed).

Treatment related effects included loose stools, urine stains, rough coats and skin lesions in both sexes receiving 18 or 54 ppm (after 20 weeks). Body weight decreases were seen in males at 18 ppm (significant from weeks 5-84) and 54 ppm (significant from week 3 until termination) and females at 54 ppm (significant from week 11 to termination).

The systemic LOEL is 18 ppm (≈0.9 mg/kg/day), based on decreased body weight gain in males. The systemic NOEL is 6 ppm (≈0.3 mg/kg/day).

ChE data indicate that inhibition of brain, plasma and RBC ChE was dose related in both sexes and occurred at all doses and sampling

times. At the highest dose tested, brain ChE was inhibited 75-80%, and plasma and RBC ChE activities were inhibited 75-91%. At the lowest dose tested (2 ppm), plasma and RBC ChE were inhibited 6-28%. There was also a slight but noticeable inhibition of brain ChE (1 month: 16% ♂ and 18% ♀; 12 months: 10% ♂; 24% ♀; 24 months: 12% ♂; 7% ♀) at 2 ppm.

The ChE LOEL is 2 ppm (≈0.1 mg/kg/day, lowest dose tested), based on brain, plasma and erythrocyte ChE inhibition. A NOEL was not established for ChE inhibition.

At the doses tested, there was no treatment-related increase in the tumor incidence when compared to controls. Dosing was considered adequate based on brain, plasma and RBC ChE inhibition.

The oncogenic NOEL is >54 ppm (≈2.7 mg/kg/day).

This chronic/carcinogenicity study in the rat is acceptable and satisfies the guideline requirement for a combined chronic/ carcinogenicity study (83-1a) in the rat (MRID Nos. 00148452 [main study]/43248102 [additional data]).

Carcinogenicity mouse study

In a carcinogenicity study, *Methamidophos technical (70% a.i.)* was administered to 50 CD-1 mice/sex/dose in the diet at dose levels of 0, 1, 5 or 25 ppm (equivalent to 0, 0.1, 0.7 or 3.6 mg/kg/day) for 106 weeks. There were no toxicological effects on mortality, behavior, hematology, organ weights, palpable masses, or histologic pathology.

Treatment related effects at 25 ppm included significant body weight decreases in both sexes (significant from weeks 72-106 ♂ and weeks 58-106 ♀), decreased body weight gain (5-10% less ♂ and 6-19% less ♀ from week 58 to 106), and significantly lower feed consumption in both sexes [significant for weeks 39, 52, 60, 78, 80, 85, 95, 100 and 106 (♂) and weeks 52 to termination (♀)].

The systemic LOEL is 25 ppm (≈3.6 mg/kg/day, highest dose tested), based on decreased body weight gain and feed consumption in males and females. The systemic NOEL is 5 ppm (≈0.7 mg/kg/day).

At the doses tested, there was no treatment-related increase in the tumor incidence when compared to controls. Dosing was, therefore, considered adequate based on adverse effects on body weight and feed consumption.

The oncogenic NOEL is >25 ppm (>3.6 mg/kg/day).

This carcinogenicity study in the mouse is acceptable and satisfies the guideline requirement for a carcinogenicity study (83-2b) in the mouse (MRID Nos. 00145579 [main study]/43248101 [additional data]).

d. Developmental Toxicity

Four developmental toxicity studies (two with rats and two with rabbits) were available for review. These data are considered adequate to assess the developmental toxicity potential of Methamidophos. For a discussion of the Food Quality Protection Act (FQPA) considerations, see Section 1.l.

Summarized findings from the four developmental toxicity studies are presented below:

Developmental toxicity rat study with 70.5% a.i.

In a developmental toxicity study, *Methamidophos technical (70.5% a.i.)* was administered by oral gavage as an aqueous solution to inseminated (mated) CD rats (24-27/group) at dose levels of 0,

0.3, 1.0 or 3.0 mg/kg/day on gestation days (GD) 6 through 15. A positive control group received 350 mg/kg hydroxyurea on GDs 9, 10 and 11. Cholinesterase activity was not measured.

Treatment-related maternal toxicity was confined to the high-dose group and included clinical signs (fasciculation, hyperactivity, salivation, lacrimation and polyuria observed on GDs 6, 7 and 8 and continued to termination); significantly decreased total and corrected for gravid uterine weight body weight gain (GDs 0-21); and significantly lower feed consumption (GDs 6-13 and 13-21). Reproductive parameters were unaffected by treatment. Treatment-related developmental effects were also only limited to the high-dose group. They were manifested as significantly decreased mean fetal body weight and total litter weights. No compound-related increases in fetal malformations or variations were seen.

The maternal toxicity LOEL is 3.0 mg/kg/day, based on decreased body weight gain and feed consumption during pregnancy and signs indicative of cholinesterase inhibition (i.e., fasciculation, hyperactivity, salivation and lacrimation). The NOEL is 1.0 mg/kg/day.

The developmental toxicity LOEL is 3.0 mg/kg/day, based on decreased fetal weight; the NOEL is 1.0 mg/kg/day.

This developmental toxicity study is acceptable and satisfies the guideline requirement for a developmental toxicity study (83-3a) in the rat (MRID No. 00148454).

Developmental toxicity rat study with 76% a.i.

In a developmental toxicity study, *MONITOR technical (76% Methamidophos)* was administered by gavage as an aqueous solution to the inseminated (mated) Sprague-Dawley rats (36/group) at nominal doses of 0, 0.04, 0.1 or 4.0 mg/kg of body weight/day. The analytically confirmed doses were 0, 0.05, 0.14 or 5.49 mg/kg of body weight/day, respectively, expressed as an active ingredient (Methamidophos). Dosing was done during gestation days (GD) 6 through 15. About 90 minutes after the last dose, blood and brain samples were taken from 6 pregnant rats/group for the determination of plasma, erythrocyte and brain cholinesterase (ChE) activities. The remaining rats were sacrificed on GD 20. Treatment-related maternal toxicity was observed only in the high-dose group and included clinical signs (tremors, muscle fasciculations and salivation), decreased body weight gain and food consumption, and inhibition of ChE activities (91, 82 and 79 % in plasma, erythrocytes and brain, respectively, relative to the control values). Treatment-related developmental effects were

observed also only in the high-dose group and included decreased placental and fetal weights (males, females and combined); an increase in skeletal variations (incompletely ossified frontal bones, sacral arches and sternebrae [segments 3, 4] and xiphoid); and unossified metacarpals and sternebrae (segment 5). Other parameters examined were unaffected by MONITOR Technical in any group.

Based on the above findings, the maternal LOEL and NOEL are 5.49 and 0.14 mg/kg/day (analytical values), respectively.

The developmental LOEL and NOEL are also 5.49 and 0.14 mg/kg/day, respectively.

The developmental toxicity study is classified as acceptable and satisfies the guideline requirement for a developmental toxicity study (83-3a) in the rat (MRID No. 43906901).

Developmental toxicity rabbit study with 62% a.i.

In a developmental toxicity study, *Monitor Technical (62% Methamidophos)* was administered by oral gavage as an aqueous solution in 0.5% Cremophor to inseminated (mated) Himalayan rabbits (15/group) at dose levels of 0, 0.1, 0.5 or 2.5 mg/kg on gestation days (GD) 6 through 18. Doses were selected on the basis of the results of a preliminary study showing weight loss and diarrhea in female rabbits (1/3) at 5 mg/kg/day. Dams were sacrificed on GD 29. Cholinesterase activity was not measured. There were no effects on mortality or clinical signs. Treatment-related maternal toxicity was manifested as reduced body weight gain at all dose levels. The response was not dose related but significant at the low and high levels. Reproductive parameters were unaffected by treatment. The number of implants, resporptions, stunted fetuses, fetal deaths, sex distribution, and fetal and placental weights were also unaffected by treatment with Monitor technical. Similarly, no compound-related increases in fetal malformations or variations were seen.

The maternal toxicity LOEL is considered to be <0.1 mg/kg/day (lowest dose tested), based on decreased body weight gain during gestation; a NOEL was not established.

The developmental toxicity NOEL is >2.5 mg/kg/day (highest dose tested).

This developmental toxicity study is acceptable and satisfies the guideline requirement for a developmental toxicity study (83-3b) in the rabbit (MRID No. 00041315).

Developmental toxicity rabbit study with 76% a.i.

In this developmental toxicity study, *Monitor® Technical (76% Methamidophos)* was administered by gavage as an aqueous solution to the timed-pregnant New Zealand White rabbits (23/group) at nominal doses of 0 (deionized water), 0.1, 0.5 and 2.5 mg/kg/day. The analytically confirmed doses were 0, 0.2, 0.65 and 2.47 mg/kg/day, respectively, expressed as Methamidophos (a.i.). Cholinesterase (ChE) activities in plasma and erythrocytes were determined on gestation day 18 only in the range-finding study. The main study contained no ChE data. Treatment-related maternal toxicity was observed in the mid-dose and high-dose groups, and included decreased body weight gain and decreased absolute (g/day) and relative (g/kg/day) food consumption. The high-dose also caused hyperactivity (thumping of the cage with the hindlimbs) and weight loss. Monitor® Technical had no effect on fetal development in this study.

Based on the above findings, the maternal LOEL and NOEL are 0.65 and 0.20 mg/kg/day (analytical values), respectively. The developmental NOEL is >2.47 mg/kg/day (HDT).

Relative to the control values, plasma and erythrocyte ChE activities in the range-finding study were inhibited at all doses of Monitor® Technical tested: 0.1-7.5 mg/kg/day (nominal); 0.2-7.73 mg/kg/day (analytical). At the LDT, the statistically insignificant inhibitions were <20%. In the remaining groups, the statistically significant inhibitions, $p<0.05$, were 44-92%.

The developmental toxicity study is classified as acceptable and satisfies the guideline requirement for a developmental toxicity study (83-3b) in the rabbit (MRID No. 44040601).

e. Reproductive Toxicity

Sufficient data were available to assess the reproductive toxicity potential of Methamidophos. For a discussion of the Food Quality Protection Act (FQPA) considerations, see Section k.l.

In a reproductive toxicity study, *Methamidophos Technical (70.5% a.i.)* was administered in the diet at 0, 3, 10 or 33 ppm (equivalent to approximately 0, 0.15, 0.5, or 1.65 mg/kg/day) to male and female CD rats (26/sex/group) over two consecutive generations. There were no treatment related effects at either the 3 or 10 ppm dietary level.

At the 33 ppm dietary level, adverse effects in parental animals included: premating body weight decrements in PO males, decreased body weight gain in PO females during gestation and lactation, decreased body weight in F1 males and females. No other treatment-related effects were seen.

Effects on reproductive performance at 33 ppm included significant reductions in the number of sperm-positive PO females delivering pups and nonsignificant 59% reduction in the number of sperm-positive F1 females delivering F2b pups.

Toxicity to the offspring at 33 ppm consisted of decreases in pup viability for the F1, F2a, and F2b generations and significant reductions in pup weight during lactation in the F1, F2a, and F2b generations.

Parental systemic

NOEL = 10 ppm (0.5 mg/kg/day)
LOEL = 33 ppm (1.65 mg/kg/day), based on decreases body weight of males and females during premating and of females during lactation.

Reproductive

NOEL = 10 ppm (0.5 mg/kg/day)
LOEL = 33 ppm (1.65 mg/kg/day), based on decreases in the number of sperm positive females giving birth.

Developmental

NOEL = 10 ppm (0.5 mg/kg/day)
LOEL = 33 ppm (1.65 mg/kg/day), based on decreases in pup viability and body weight during lactation.

This study is classified as acceptable and satisfies the guideline requirement (83-4) for a two-generation reproductive toxicity study in the rat (MRID No. 00148455 [main study]/41234301 [additional data]).

In a 2-generation reproduction study, Methamidophos technical, only 73% a.i., was administered to 30 Sprague-Dawley rats/sex/dose in the diet at levels of 0, 1, 10 and 30 ppm. However, based upon actual mean analyses of the dose preparations and correction for % a.i., dietary levels would be equivalent to 0, 0.73, 7.14, and 19.06 ppm. These corrected dose levels appear more realistic since they take into account both mean analytical determinations as well as the relatively low levels of active ingredient (the percent of

active ingredient was intentionally maintained at such a low level due to the hygroscopic nature of the active ingredient, Methamidophos). During the premating growth period, corrected dose levels of Methamidophos were 0, 0.08, 0.66, and 1.76 mg/kg/day. However, during the lactation period corrected dose levels were 0, 0.15, 1.10, and 2.85 mg/kg/day reflecting the highest dose levels during the study. In this reproduction study, plasma, RBC, and brain cholinesterase inhibition were also assessed in adult and weanling rats.

During the growth phase, mean body weights of F1 adult males were reduced in both the 10 and 30 ppm dietary levels. Food consumption was also consistently increased in P and F1 males over the majority of weeks sampled. Terminal body weights were statistically reduced in 30 ppm P males and 10 and 30 ppm F1 males. Cholinesterase inhibition was evident at all dose levels. These findings included statistically significant RBC inhibition in the 1 ppm P males which reflected greater than a 20% inhibition as compared to control values, statistically reduced RBC cholinesterase in F1 males, and significantly reduced brain cholinesterase in P and F1 females at 1 ppm, the lowest dose tested. **Based on RBC and brain cholinesterase inhibition at the LDT of 1 ppm, a NOEL for parental systemic toxicity was not determined in this study. The NOAEL is <1 ppm (<0.73 ppm [0.08 mg/kg/day] if corrected for actual analytical concentration and percent a.i.)**

Methamidophos administration was associated with significantly reduced pup weights at the 1 ppm, 10 ppm, and 30 ppm dose levels during the F1a lactation period, in the 10 ppm and 30 ppm levels in the F1b and F2b lactation periods, and in the 30 ppm level in the F2a lactation period. Additionally, plasma, RBC and brain cholinesterase were significantly reduced at the 30 ppm dose level in pups on postnatal day 4 and at the 10 and 30 ppm dose levels in weanling pups (postnatal day 21). Also, the number of stillborn pups was increased at the 30 ppm level, and pup survival throughout lactation was decreased at this dose level. This is further demonstrated by a decrease in the lactation index during the F1a, F1b, and F2b matings at the high dose. The number of pups cannibalized at the 30 ppm level was also significantly increased. **Based on pup body weight decrements at the LDT of 1 ppm, it is concluded that no NOEL for offspring toxicity was determined in this study. The NOAEL is < 1 ppm (<0.73 ppm [0.08 mg/kg/day] if corrected for actual analytical concentration and percent a.i.)**

This reproduction study in the rat is classified as **acceptable.** This study satisfies the guideline requirement for a two-generation reproduction study (OPPTS 870.3800, §83-4) in the rat,

although no NOAEL's for parental and offspring toxicity were determined in this study. This study is considered acceptable based on the finding that the effects observed in the offspring at the low dose level appear to be a threshold effect. While the effects relative to cholinesterase inhibition in parental animals are clearly apparent at all dose levels, the fact that there is no NOAEL for a parental effect is not a requirement relative to acceptability of the study for regulatory purposes since the primary purpose of the study is to investigate reproductive and offspring toxicity (MRID Nos. 44466001[main study]/ 44815401 and 44815402 [additional data]).

f. Mutagenicity Studies

Sufficient data are available to satisfy the data requirements for mutagenicity. Results from the five acceptable studies indicate that Methamidophos is not mutagenic in bacteria but does induce gene mutations in cultured mammalian cells at high S9-activated doses. Similarly, there was evidence of clastogenicity at high nonactivated concentrations and polyploidy at high S9-activated levels. In contrast, Methamidophos was negative for chromosome aberrations in vivo and did not induce UDS in vitro. The data suggest, therefore, that the marginal genotoxicity activity seen with Methamidophos is not expressed in vivo. The lack of an oncogenic effect in the rat or mouse long-term feeding studies and the absence of significant reproductive or developmental toxicity that could be associated with a mutagenic mode of action (i.e., germ cell damage, reduced numbers of pregnancies, decreased total implants, increased resorptions) support this conclusion. Based on these considerations, there is no concern for mutagenicity.

Summarized findings supporting the above conclusions from the mutagenicity studies are presented below:

f.1 Gene Mutations

Salmonella typhimurium reverse gene mutation assay: The test was negative up to the highest dose of *Methamidophos (Monitor technical, purity not stated)* that was investigated with or without S9 activation (10,000 µg/plate). The study is classified as acceptable and satisfies the guideline requirements (84-2) for a bacterial gene mutation assay (MRID No. 00098457).

Chinese hamster ovary (CHO) cell HGPRT forward gene mutation assay: The test was negative up to the highest nonactivated dose tested (5000 µg/mL); however, *Methamidophos (75.6%)* induced dose-related increases in the mutation frequency (MF) at 4000 & 5000 µg/mL +S9. This study is classified as acceptable and satisfies the guideline requirements (84-2) for an in vitro mammalian cell gene mutation assay (MRID No. 42854701). Although the evidence of mutagenesis is considered weak, it is consistent with the findings of a previously conducted CHO/HGPRT assay (MRID No. 42013701). This study is classified as unacceptable and does not satisfy the guideline requirements (84-2) for an in vitro mammalian cell gene mutation assay because definitive conclusions could not be reached regarding the slight increases in the MF at high S9-activated doses of Methamidophos.

f.2 Chromosome Aberrations

In vitro chromosome aberrations in CHO cells: The test was positive; reproducible and significant increases in structural chromosome aberrations were obtained at 4200 and 5140 µg/mL *Methamidophos (74.5%)* without S9 but only after 20 hours of continuous exposure. In the presence of S9 activation, there was no indication of a clastogenic response; however, non- dose-related increases in polyploidy were noted at 3150, 4200 & 5250 µg/mL. This study is classified as acceptable and satisfies the guideline requirements (84-2) for an in vitro mammalian cell cytogenetic assay (MRID No. 41461401).

In vivo bone marrow cytogenetic assay: The test was negative in CD-1 male and female mice receiving a single oral gavage exposure to *Methamidophos (74.4%)* doses ranging from 0.6-12 mg/kg. Toxic signs, consistent with cholinesterase poisoning, were observed at 6, 9 and 12 mg/kg. Lower concentrations (2 mg/kg) were not overtly toxic and there was, no evidence of a cytotoxic effect on the target cell at any dose. This study is classified as acceptable and satisfies the guideline requirements (84-2) for an in vivo cytogenetic assay (MRID No. 41234306).

f.3 Other Mutagenic Mechanisms

In vitro unscheduled DNA synthesis in primary rat hepatocytes assay: The test was negative up to cytotoxic doses (>1 µL/mL) of *Methamidophos (71.2%)*. This study is classified as acceptable and satisfies the guideline requirements (84-2) for an UDS assay (MRID No. 41234305).

g. Metabolism

In a metabolism study, female Sprague Dawley rats received single oral doses of 0.16-0.19 mg (0.43-0.51 µC, respectively) of radiolabeled *Monitor technical (S-methyl-^{14}C Methamidophos, ≥99.5%)* and were sacrificed 5-9 days after treatment. Urine, feces and CO_2 were collected twice daily and brain, kidney, liver, heart, spleen, femur bone, blood and fat were analyzed for radioactivity. For studies with the ^{32}P-labeled test substance, groups of two male and two female Sprague Dawley rats were preconditioned for 2 weeks with 0.5 mg/kg nonradioactive Monitor technical followed by daily dosing with 0.21 mg (2.72 µC) of radiolabeled *Monitor technical (^{32}P Methamidophos, ≥99.5%)* for 1, 3, 7, 14, 21 or 28 days. Urine and feces were collected and the distribution of radioactivity was assessed in kidney, liver, heart, muscle (from the carcass) and carcass fat.

Monitor technical was rapidly degraded and/or eliminated within the first 24 hours postdosing. In the ^{14}C studies, 60% of the radioactivity was detected in CO_2 and 11% in urine. Fecal excretion of radiolabel was low. In the ^{32}P studies, ≈70% of the radioactivity was detected in the urine. Fecal excretion of the ^{32}P radiolabel was initially low (2-3%) but increased 3-21 days postdosing (8-21%). The identified metabolites in the urine (O,S-dimethyl-phosphorothioate, methyl dihydrogen phosphate and phosphoric acid) are not considered to be ChE inhibitors. The content of Monitor technical in tissue 14 days posttreatment was <0.004 ppm. There was no difference in the rate of metabolism, excretion or nature of the metabolites between males and females.

This metabolism study is classified acceptable-nonguideline; it does not satisfies the current guideline requirement (85-1) for a metabolism study. However, the available data do allow the basic characterization of the metabolism of Methamidophos (MRID No. 00015224).

h. Neurotoxicity Studies

Acceptable acute and subchronic delayed neurotoxicity in hens and acute and subchronic neurotoxicity screening batteries in rats were available for review. There were no data gaps for the assessment of the neurotoxic potential of Methamidophos. Data from the hen studies indicate that Methamidophos produces toxic signs characteristic of ChE inhibition (acute and subchronic exposures), inhibition of ChE and neurotoxic esterase (NTE) activity in brain and spinal cord (subchronic exposure) but no delayed neurotoxicity or histological changes in brain, spinal cord or peripheral nerves. In rats, methamidophos induced neurobehavioral effects and ChE inhibition following both acute and subchronic exposure. There were, however, no treatment-related gross or histopathological effects and brain weights were unaffected by treatment. Neurobehavioral effects in both the acute and subchronic studies occurred at doses that were only slight higher than the lowest dose at which ChE inhibition was detected. Special studies conducted with Methamidophos (racemate and enantiomers) showed evidence of delayed neurotoxicity in hens following ingestion of high doses (12-16x the oral LD_{50}). Similarly, information in the open literature indicated that Methamidophos can cause delayed neurotoxicity in humans following exposure to excessive, life threatening concentrations.

The following summaries present the relevant findings from the acute and subchronic neurotoxicity studies which support these conclusions:

h.1 Studies in Hens

Acute oral delayed neurotoxicity study in hens

In an acute oral delayed neurotoxicity study, White Leghorn hens were exposed to *Monitor technical (Methamidophos, 74% a.i.)*. In the preliminary study (acute oral lethality), groups of six hens received single oral doses of 10, 15, 22.5, 33.75, 50.63 or 75.94 mg a.i./kg and were observed for 42 days. In the neurotoxicity study, animals were dosed orally with 30 (10 hens) or 50.63 mg a.i./kg (12 hens) and atropine sulfate (50 mg/kg) on day 0. Survivors were re-dosed on day 21. As a positive control, 10 hens were administered 500 mg/kg tri-o-cresylphosphate (TOCP) and 16 hens served as untreated controls. Neither forced motor activity nor neurotoxic esterase (NTE) were assessed.

In the oral lethality phase of the study, deaths (>2 hours-6 days) and other signs of toxicity were observed at 22.5 mg/kg. Acute signs of poisoning included: muscular weakness, unsteadiness (leg weakness), diarrhea, excessive salivation, anorexia, lateral and sternal recumbency, dyspnea, and cyanotic combs and wattles shortly before death. The higher the dose, the sooner the onset of toxic signs and death. Death was caused by respiratory paralysis. No signs of toxicity were observed at 10 or 15 mg/kg.

Based on these findings, the **oral LD_{50} in hens = 29.75 mg/kg.**

In the neurotoxicity phase of the study, no signs of delayed toxicity or histopathological lesions typical of delayed neurotoxicity were observed at 30 or 50.63 mg/kg. Two of 10 hens died at 30 mg/kg and 4/12 hens died at 50.63 mg/kg. Signs of delayed toxicity and histopathological lesions typical of delayed neurotoxicity were observed in 7/10 positive control hens dosed with 500 mg/kg TOCP.

This acute delayed neurotoxicity study is classified acceptable; it satisfies the guideline requirement for an acute delayed neurotoxicity study (81-7) in the hen (MRID No. 00041317).

Subchronic oral delayed neurotoxicity study in hens

In a subchronic delayed neurotoxicity study, SRA 5172 *(Methamidophos 76% a.i)* was administered to 16 White Leghorn hens/dose by oral gavage 5 days/week for 3 months at dose levels

of 0, 0.3, 1 or 3 mg/kg/day. The highest dose tested (3 mg/kg/day) was based on the results of a preliminary study. Treatment-related findings observed in the 3 mg/kg/day group included somnolence, emaciation, weight loss (22%), and significant inhibition of butyrylcholinesterase (BuChE) activity in plasma at weeks 4, 8 and 12 (average of all means = 48%) and NTE activity in brain (17%) and spinal cord (42%). At 1 mg/kg/kg, no clinical signs or weight loss were noted. A nonsignificant inhibition (23%) of plasma BuChE was seen at week 4 and significant inhibition was reported for this dose group at week 8 (27%); the average of all means was 22% but not significant. Also at 1 mg/kg/day, NTE activity was significantly inhibited in the spinal cord (22%) but not the brain (2%). No effects on clinical signs, body weight, plasma BuChE or NTE occurred at 0.3 mg/kg/day.

Overall, the data indicate that BuChE inhibition was dose related in the mid- and high-dose groups; the peak response appeared to occur at week 8. Similarly, NTE inhibition was dose related at 1 and 3 mg/kg/day. However, ataxia, abnormal motor activity or histological changes in brain, spinal cord and peripheral nerves, generally regarded as indicators of delayed neurotoxicity, were not observed in any hen on the study. Based on the negative results of the forced motor activity tests and microscopic examinations of brain, spinal cord and peripheral nerves, SRA 5172 did not induce delayed neurotoxicity in hens.

LOEL = 1 mg/kg/day based on inhibition of plasma BuChE and spinal cord NTE activity.

NOEL = 0.3 mg/kg/day.

This subchronic toxicity study is classified acceptable and satisfies the guideline requirement for a subchronic delayed neurotoxicity study (82-5 a) in hens (MRID No. 40985202).

h.2 Studies in Rats

Acute neurotoxicity screening study in rats

In an acute neurotoxicity screening study, *Methamidophos technical (≈76%)* was administered in a single gavage dose to 24 male and 24 female Sprague-Dawley rats at 0, 1, 3 or 8 mg a.i./kg. Actual concentrations, based on analytical determinations, were 0.9, 3, or 9 mg a.i./kg, respectively. At 1 mg/kg, males had slightly decreased motor/locomotion activities (-23 to -25% less than controls but not statistically significant) and one male had clinical signs (increased sitting/lying; urine, oral and nasal

staining). Females at this dose showed slightly reduced motor activity (-26%) during the first interval. At 3 mg/kg, markedly decreased motor/locomotor activity (-84 to -96%), repetitive chewing, uncoordinated gait, muscle fasciculations, impaired righting reflex, decreased forelimb grip strength (80% of control), decreased activity and rearing, increased ease of removal from cage and decreased body temperature were observed. Males at 3 mg/kg also had ataxia, reduced approach or touch response and increased SGOT activity (143% of control), and females had increased lateral recumbency and tremors and decreased triglycerides (56% of control). At 8 mg/kg, salivation, flattened posture, reduced clicking sound or tail pinch responses and increased SGPT (170-181% of control) were observed. Males also had tremors and increased serum cholesterol (130% of control) and females had decreased hindlimb grip strength (71% of control), reduced approach and touch response and increased SGOT (670% of control). Most clinical signs were observed only on the day of dosing and were completely resolved by study day 5. The peak effect on the functional observational battery (FOB) and motor and locomotor activities occurred on day 0. No treatment related gross or histopathological effects were seen; brain weights were unaffected by treatment.

The LOEL is 0.9 mg/kg (analytical value), based on slightly reduced motor/locomotor activity in males and females and clinical signs in one male consistent with neurotoxicity secondary to cholinesterase inhibition. The study NOEL is <0.9 mg/kg.

Statistically significant and dose-related inhibition of serum, RBC and brain ChE was observed at all doses and in both sexes. At 1 mg/kg, ChE activity was -24% to -39% less than control, increasing to -67% to -81% at 3 mg/kg and -82% to -92% at 8 mg/kg.

The ChE LOEL is 0.9 mg/kg (analytical value), based on inhibition of all measured activities. The ChE NOEL is 0.9 mg/kg. Although NOELs were not established, a second rat acute neurotoxicity study on Methamidophos (MRID No. 43345801) demonstrated a LOEL = 0.7 mg/kg (and threshold ChE NOEL = 0.3 mg/kg).

This acute neurotoxicity study is classified acceptable; it satisfies the guideline requirement for an acute neurotoxicity study (81-8) in the rat (MRID No. 43025001).

Acute neurotoxicity screening study in rats
(Supplemental study)

In an acute (supplemental) neurotoxicity screening study, *Methamidophos (75.6% a.i.)* was administered in a single gavage

dose to 18 male and 18 female Sprague-Dawley rats at 0, 0.3 and 0.7 mg a.i./kg (analytical values; nominal values: 0, 0.3 and 0.6 mg a.i./kg, respectively). Twelve rats/sex/dose were assessed for neurobehavioral functions at about 2 hours postdosing and on days 7 and 14. Six rats/sex/dose were used for the determination of cholinesterase (ChE) activities in plasma and erythrocytes at ≈2 weeks before dosing, and in plasma, erythrocytes and brain at about 2 hours after dosing; ChE activities were not measured during the remaining 13 days. Other parameters examined were clinical observations and body weights. Gross necropsy and histopathology were not performed because nothing remarkable was observed in another (main) rat acute neurotoxicity screening study at 9.0 mg of Methamidophos (a.i.)/kg (confirmed analytical dose) (MRID No. 43025001).

Relative to the control values, Methamidophos at 0.3 mg/kg had no effect on any of the parameters examined. The 24% inhibition of plasma ChE activity for the females in this group was not statistically significant and was due to an unusually high control value. This finding was, therefore, not regarded as biologically relevant.

Relative to the control values, the 0.7 mg/kg dose had no effect on the neurobehavioral parameters examined, but the ChE activities were inhibited significantly (p 0.05) in males and females (M/F) on day 0 as follows: erythrocytes (21/26%), plasma (27/25%) and brain (15/26%).

This study should be considered together with another acute neurotoxicity study (MRID No. 43025001) in which a NOEL for neurobehavioral effects was not determined. Based on the results of both studies, the NOEL for neurobehavioral effects is 0.7 mg/kg and the LOEL is 0.9 mg/kg (analytical value; nominal value = 1.0 mg/kg), for males and females. The NOEL and LOEL for ChE activities are 0.3 mg/kg and 0.7 mg/kg, respectively.

This study (MRID No. 43345801), considered together with the first study (MRID No. 43025001), is classified as acceptable and satisfies the guideline requirement for an acute neurotoxicity screen (81-8) in the rat.

Subchronic neurotoxicity screening study in rats

In a subchronic neurotoxicity screening study, *Methamidophos technical (75.6-75.8%)* was administered in the diet for 13 weeks to 18 male and 18 female Fischer 344 rats/group at nominal levels of 0, 1, 12 or 60 ppm a.i. (analytical concentrations were 0, 1, 12 or 59 ppm a.i., respectively). Dose selection was based on the

results of subchronic and chronic feeding studies. The doses used in this subchronic neurotoxicity screening study were equivalent to 0, 0.067, 0.787 or 4.25 mg/kg/day, respectively (♂) and 0, 0.074, 0.899 or 4.94 mg/kg/day, respectively (♀). Treatment-related clinical signs in males and females of the high-dose group included: muscle fasciculations, increased reactivity, perianal and urine staining, and red and clear lacrimation; tremors were also noted in the high-dose males. Reductions in motor and locomotion activities (26-57% of controls - statistically significant in males at all test intervals and females during week 4) and decreased forelimb grip strength (14-31% of control - statistically significant in males at all test intervals and females during weeks 8 and 13) were also reported. There was no evidence of cumulative toxicity beyond week 8. Reduced activity (sluggish arousal during open field observations) was only seen in the high-dose females. Decreased body weight gain was also recorded for the high-dose males (11%) and females (17%).

Mid-dose females had an increased incidence of urine stains throughout most of the study. Other treatment-related effects in the mid-dose group were: reduced motor and locomotor activities (17-32% of control--both sexes) and decreased body weight gain in the females (10%).

No treatment-related effects on clinical signs, motor and locomotor activities, FOB or body weight were observed in the low-dose group. Similarly, treatment with Methamidophos had no adverse effects on the incidence of gross or microscopic changes or brain weights.

Based on these findings, the NOEL for neurotoxicity is 1 ppm (0.067 mg/kg/day for males and 0.074 mg/kg/day for females). The LOEL for neurotoxicity is 12 ppm (0.787 mg/kg/day for males and 0.889 mg/kg/day for females).

The ChE data indicate that inhibition of plasma and RBC ChE was statistically significant and dose related in both sexes at the mid- and high-dose and at both sampling times (weeks 4 and 13). Significant inhibition of plasma ChE was also observed in low-dose females at week 4. Brain ChE inhibition was dose related and significant in males of all treatment groups and females of the mid- and high-dose groups. At the highest dose tested (59 ppm, analytical value), brain ChE was inhibited 84-86%, plasma ChE inhibition ranged from 74-91% and RBC ChE ranged from 79-98%. In the mid-dose group, brain ChE was inhibited 58-60%, plasma ChE was suppressed 41-64% and RBC ChE activity was inhibited 70-77%. At the lowest dose tested (1 ppm, analytical value), brain ChE was inhibited by 6%, plasma ChE by 6-26% and RBC ChE by 1-9%.

Based on these findings, the NOELs and LOELs for inhibition of ChE (both sexes) were:

RBC: NOEL = 1 ppm (0.067 mg/kg/day ♂; 0.074 mg/kg/day ♀)
LOEL = 12 ppm (0.787 mg/kg/day ♂; 0.899 mg/kg/day ♀)

Plasma and brain = NOEL = <1 ppm (<0.067 mg/kg/day ♂; <0.074 mg/kg/day ♀, lowest dose tested)
LOEL = 1 ppm

This subchronic neurotoxicity study is classified acceptable; it satisfies the guideline requirement for a subchronic neurotoxicity screen (82-7) in the rat (MRID No. 43197901).

h.3 Special Studies with Methamidophos: Racemate and Enantiomers

Methamidophos is a racemic mixture of two stereoisomers: dextrorotary D (+) and levorotary L (-). This racemic mixture, Methamidophos (+/-), can be separated into the individual isomers (enantiomers): Methamidophos (+) and Methamidophos (-). The three compounds were the subject of the special studies summarized below:

In an acute oral toxicity study, the LD_{50}s for male Wistar rats were: Methamidophos (+/-): 16 mg/kg; (+) isomer: 14 mg/kg; and (-) isomer: 16 mg/kg. Toxic signs characteristic of ChE inhibition were seen with all three test materials (MRID No. 41685802).

In an acute oral toxicity study, the LD_{50}s for hens were: Methamidophos (+/-): 25 mg/kg; (+) isomer: 43 mg/kg; and (-) isomer: 82 mg/kg. Toxic signs characteristic of ChE inhibition were seen with all three test materials (MRID No. 41685803).

In a neuropathy target esterase (NTE) study in hens, inhibition of NTE activity in the brain was: 66% at twice the LD_{50} (50 mg/kg) for Methamidophos (+/-) with 89% of the inhibited NTE being reactivated in an unmodified (unaged) form. For the Methamidophos (+) isomer, NTE was inhibited 98% at ten times the LD_{50} (400 mg/kg) with 86% of the inhibited NTE being reactivated in an unaged form. For the Methamidophos (-) isomer, NTE was inhibited by 58-84% at five times the LD_{50} (400 mg/kg) with 27% of the inhibited NTE being reactivated in an unaged form. Approximately 73% of the inhibited NTE was modified (aged). Based on the marked percentage of aged NTE, the (-) isomer could be considered a possible trigger for organophosphorus esterase-induced delayed polyneuropathy (OPIDP) (MRID No. 41685804).

In an OPIDP study in hens, Methamidophos (+/-) was positive for OPIDP at 400 mg/kg (16x LD_{50}); the Methamidophos (+) isomer was positive for OPIDP at 400 mg/kg (9x LD_{50}); and the Methamidophos (-) isomer was negative for OPIDP at 400 mg/kg. However, only two hen were available for the assessment of OPIDP with the (-) isomer (MRID No. 41685805).

h.4 Information from the Open Literature

Based on an earlier review of data in the open literature from 1961-1980, ingestion of high doses of Methamidophos (usually suicide attempts but occasionally by accident) can cause delayed neurotoxicity (polyneuropathy) in humans. Similarly, adult hens develop polyneuropathy but only after ingesting Methamidophos levels equivalent to 12-16 times the LD_{50}. Based on these considerations, it was concluded that Methamidophos does have delayed neurotoxic potential but only at excessive, life threatening concentrations (MRID No. 41685801).

A survey of the more recent literature supports the above statement that exposure to high doses of Methamidophos (through accidental occupational poisonings, suicide attempts, or ingestion of contaminated vegetables) can cause delayed peripheral neuropathy. McConnell et al. (1994) cite evidence of abnormal vibrotactile thresholds in Nicaraguan agricultural workers previously poisoned with Methamidophos.

j. Domestic Animal Safety Study:

Based on the use pattern of Methamidophos, this study is not required because it is unlikely that there would be a significant exposure for domestic animals.

k. Toxicology Endpoints of Concern for Use in Risk Assessments

On January 20, 1998, the Health Effects Divison's Hazard Identification Science Assessment Review Committee (HAZ ID SARC) evaluated the toxicology data base of Methamidophos to re-assess the Reference Dose and determine the Uncertainty Factor (UF) and/or Margin of Exposure (MOE) for dietary and non-dietary exposure risk assessments. The Committee also addressed the potential sensitivity of infants and children as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions are presented below:

k.1. Special Sensitivity to Infants and Children

Pursuant to the language and intent of the FQPA directives regarding infants and children, the applicable toxicity data base for Methamidophos was evaluated by the HED Hazard Identification SARC. The SARC concluded the following:

Adequacy of Data: There are no data gaps for the assessment of the effects of Methamidophos following *in utero* and/or early postnatal exposure. Suitable studies for this assessment are: (1) developmental toxicity studies in rats (MRID Nos. 00148454 and 43906901); (2) developmental toxicity studies in rabbits (MRID Nos. 00041315 and 44040601); and (3) two generation reproductive toxicity study in rats (MRID Nos. 00148455 and 44466001).

Susceptibility Issues: There is no indication of an increased sensitivity of the offspring of rats or rabbits to prenatal and postnatal exposure to Methamidophos. In all studies examined, maternal or parental NOELs are lower or equivalent to the offspring NOELs.

Recommendations for a Developmental Neurotoxicity Study: Based on a weight-of-the evidence evaluation, the Hazard Identification SARC determined that an assessment of functional development is necessary to fully characterize the effects of Methamidophos exposure on perinatal animals; therefore, a developmental neurotoxicity study in rats with methamidophos is **required**. The following information was considered in support of this decision:

Methamidophos is a neurotoxic chemical and there is a concern for the structure-activity relationships (SAR) of this chemical class (organophosphorus pesticides).

Administration to various species (rat, dog and human) results in ChE inhibition. Frank neurobehavioral observations generally occur at a level that is only slightly higher than the dose at which ChE inhibition is first observed.

Methamidophos is acutely lethal at relatively low doses, with an oral LD_{50} of approximately 16 mg/kg in the rat.

In studies in the open literature (MRID No. 41685801; McConnell et al., 1994; Zheng, 1990; Senanayake and Johnson, 1982), Methamidophos ingestion has been shown to result in delayed peripheral neuropathy in humans and polyneuropathy in hens, albeit at extremely high doses (in excess of the hen LD_{50}). It was recognized by the SARC, however, that levels

causing delayed neuropathy in humans are not well characterized.

Dose-related and significant NTE inhibition was seen at 1 and 3 mg/kg/day in the subchronic neurotoxicity study (MRID No. 40985202) in hens. Similarly, NTE inhibition has been reported at high doses in acute studies from the open literature (MRID No. 41685801; Lotti et al., 1995).

Safety Factor: The Hazard Identification SARC determined that, for Methamidophos, the 10-fold safety factor (SF) for the protection of infants and children **should be reduced to 3x** based on the following considerations:

There is no indication of an increased sensitivity of the offspring of rats or rabbits to prenatal and postnatal exposure to Methamidophos.

The toxicology data base is complete (i.e, no data gaps for standard Subdivision F Guideline requirements).

However,

There is evidence of positive NTE in hens from both submitted studies and studies in the open literature.

Positive OPIDN has been demonstrated in studies conducted in hens and in humans.

A weight-of-the evidence evaluation of the data base indicates the need for evaluation of functional development and thus a need to conduct a developmental neurotoxicity study.

k.2 Reference Dose (RfD) for Methamidophos (Chronic Dietary Exposure)

Methamidophos was first presented to the Reference Dose (RfD)/Peer Review Committee in 1986; the RfD established at that time (0.00005 mg/kg/day) was reconsidered by the RfD Committee in April 1987 and verified in May 1987. The RfD Committee met on May 29, 1992 and established an RfD of 0.001 mg/kg/day. This value was based on the threshold LOEL 0.5 ppm (0.03 mg/kg/day) for the inhibition of plasma, RBC and brain ChE in an 8-week feeding study with rats (special ChE inhibition study, MRID No. 41867201) and an uncertainty factor (UF) of 30 (10x to account for intra-species differences and 3x to account for the lack of a NOEL). The RfD

Committee did not consider it necessary to apply the customary 10x for inter-species extrapolation because of the existence of human data with Methamidophos and the related compound, Acephate. Additionally, the RfD Committee concluded that the 10x UF generally applied to estimate an RfD derived from a subchronic study was not necessary for Methamidophos because both the magnitude and severity of ChE inhibition were comparable in the subchronic and chronic studies. On January 20, 1998, the Health Effects Division HAZ ID SARC carefully reevaluated all appropriate data and determined that the dose of 0.03 mg/kg/day in the 8-week rat study is a NOEL and not a threshold LOEL. Thus, there is no need to apply an additional UF (i.e., 3x). However, the conventional 10x UF to account for inter-species extrapolation should be applied because the available human data were not considered adequate to support the removal of this UF. Additionally, an FQPA factor of 3x (see above) should be applied. Thus, the Hazard Identification SARC concluded that for chronic dietary risk assessment, an UF of 300 is required, which includes 10x for inter-species extrapolation, 10x for intra-species variation and 3x based on FQPA considerations. The RfD is 0.0001 mg/kg/day, based on an 8-week feeding study (MRID No. 41867201) with a NOEL of 0.03 mg/kg/day and an UF of 300.

k.3 Acute Dietary Exposure

In an acute neurotoxicity study, groups of Sprague-Dawley rats (24/sex/dose) received a single oral (gavage) administration of Methamidophos at 0, 1, 3 or 8 mg a.i/kg (actual concentrations, 0, 0.9, 3 or 9 mg a.i./kg. respectively) (MRID No. 43025001). In another acute neurotoxicity study, groups of Sprague-Dawley rats (18/sex/dose) received a single oral (gavage) administration of Methamidophos at 0, 0.3 and 0.6 mg a.i/kg (actual concentrations, 0, 0.3 or 0.7 mg a.i./kg., respectively) (MRID No. 43345801). From the results of both studies, the NOEL is 0.3 mg/kg based on the inhibition of ChE activities in plasma, RBC and brain in male and female rats after a single dose of 0.7 mg/kg (LOEL). The NOEL of 0.3 mg/kg is selected for the acute dietary risk assessment. An MOE of 300 is needed for risk assessment which includes 10x for inter-species extrapolation, 10x for intra-species variation and 3x based on FQPA considerations.

k.4 Dermal Absorption

Dermal absorption studies are not available and the submitted dermal studies are unacceptable. However, a 21-day dermal study in rats was submitted and was used by the, the Hazard Identification Assessment Review Committee (HIARC) for the dermal risk assessments. It should be noted, however, that the actual concentrations of the active ingredient (ai) were not available at the time the HIARC met or during the preparation and release of the Toxicology Chapter and the RED document. These data were submitted by the registrant on September 29, 1998. The review of these data in the submitted supplemental report (Addendum to MRID No. 44525301) indicated that dose levels of 1, 15 and 50 mg/kg/day, when corrected for actual concentration of the active ingredient (ai), were 0.749, 11.2 and 36.5 mg/kg/day, respectively. Accordingly, the selected NOEL of 1.0 mg/kg/day based on plasma, red blood cell and brain ChEI for the Short-and Intermediate-Term dermal risk assessments has been revised to 0.749 mg/kg/day to correct for the ai (see HED Document No.013394).

k.5 Short-Term (1-7 days) Occupational and Residential Exposure and Intermediate-Term (1 week to several months) and Long-Term (several months to lifetime) Occupational and Residential Exposure

In a 21-day dermal toxicity study, Methamidophos Technical (76.9 to 80.5% a.i.)] was administered to 9 to 10 male and female Sprague-Dawley rats dermally in pH 7.3 phosphate buffer solution (dose volume of 1 ml/kg of body weight) at dose levels of 0, 1, 15, and 50 mg/kg/day.

Since the Technical material has a relatively low concentration of active ingredient, dose levels corrected in terms of active ingredient are significantly lower. The corrected dose levels would then be 0.749, 11.2, and 36.5 mg/kg/day. These dose levels should be utilized for risk assessment purposes.

No compound related effects on mortality, clinical signs, body weight, food consumption, or gross and histopathology were apparent at any dose level. Dose related plasma, RBC and brain cholinesterase inhibition were noted at 15 and 50 mg/kg/day of technical. A statistically significant increase in relative lung weights was observed at the high dose males, but this was not supported by histopathologic findings. Therefore, the LOEL is 15 mg/kg/day technical (corrected for active ingredient, this dose is equivalent to 11.2 mg/kg/day) based on brain, RBC and plasma cholinesterase inhibition. The NOEL, which is 1 mg/kg/day technical (equivalent to a corrected dose for active ingredient of 0.749 mg/kg/day), is selected for the short-term dermal assessment. An MOE of **100** is needed for the risk assessment which includes 10x for inter-species extrapolation and 10x for intra-species variation.

k.6 Long-Term (several months to lifetime) Occupational and Residential Exposure

The use pattern does not indicate long-term dermal exposure; therefore, this risk assessment is NOT required.

k.7 Short-Term, Intermediate-Term and Long-Term Inhalation Exposure

In a subchronic inhalation toxicity study, Wistar rats (10/sex/group) were exposed to aerosol concentrations of Methamidophos at 0, 1.1, 5.4 and 23.1 mg/m^3 (0, 0.001, 0.005 and 0.023 mg/L, respectively (MRID No. 41402401). The NOEL is 0.001 mg/L based on plasma, erythrocyte and brain ChE inhibition at 0.005 mg/L (LOEL). The NOEL of 0.001 mg/L is selected for all exposure periods because this value is derived from the only study available for the inhalation risk assessments. An MOE of 100 is needed for the risk assessment which includes 10x for inter-species extrapolation and 10x for intra-species variation.

k.8 Classification of Carcinogenic Potential

The Health Effects Division Reference (RfD)/Peer Review Committee, which met on June 15, 1995, reviewed the data from the combined chronic/carcinogenicity feeding study in rats (MRID Nos. 00148452/43248102) and the carcinogenicity feeding study in mice (MRID Nos. 00145579/43248101) and concluded that the doses used in the chronic rat and mouse studies were adequate to assess the potential carcinogenicity of Methamidophos in these species. It was further concluded that Methamidophos did not alter the spontaneous tumor profile in rats or mice. Based on these deliberations, Methamidophos was classified in **"Group E"** (i.e., the chemical is characterized as **"Not Likely"** to be carcinogenic in humans via relevant routes of exposure).

k.9 Aggregate Risks: For the aggregate exposure risk assessment, the MOE's derived for the oral, dermal and inhalation exposures may be combined to obtain a total MOE since a common toxicological endpoint (i.e., ChE inhibition) was observed in oral, dermal and inhalation toxicity studies/routes. However, since there are no residential uses for methamidophos, the totoal MOE was derived using the following formulae:

$$\text{Total MOE:} \quad \frac{1}{\frac{1}{MOE_{Inhalation}} + \frac{1}{MOE_{Dermal}}}$$

l. Toxicity Data Gaps

There are no data gaps for standard Subdivision F Guideline requirements for Methamidophos; however, the SARC has determined that a developmental neurotoxicity study in rats is required.

REFERENCES

GUIDELINE NUMBER	MRID NUMBER	CITATION
81-1	00014044	Cavalli, R.D., Hallesy, D.W. (1968). The Acute Toxicity of RE 9006 (95%) in Rats. Report No. SOCO 14/I:87 CDL: 093265-B; received March 5, 1970 under OF 0956. Unpublished study submitted by Chevron Chemical Co., Richmond, CA.
81-1	41685802	Flucke, W. (1990). Methamidophos (Racemate and Enantiomers): Study for Acute Oral Toxicity to Rats; Bayer AG, Wuppertal, Germany; Report No. 100278; Report Issued May 4, 1990. Unpublished study submitted by Mobay Corp., Kansas City, MO.
81-2	00014049	Cavalli, R.D., Hallesy, D.W. (1968). Acute Dermal Toxicity of Monitor Technical: Report No. SOCO 30/I:121-8 CDL: 093265-G; received March 5, 1970 under OF 0956. Unpublished study submitted by Chevron Chemical Co., Richmond, CA.
81-3	00148449	Sangha, G. K. (1984). Acute Inhalation Toxicity Study with Technical Methamidophos (Monitor®) in Rats; Mobay Chemical Corp., Stilwell, KA; Study No. 84-041-02; Report Issued September 11, 1984; Unpublished study submitted by Mobay Chemical Corp., Kansas City, MO.
81-4	00014221	Rittenhouse, J.R. (1977). The Eye Irritation Potential of Monitor Technical; Standard Oil Co. of CA; Report No. SOCAL 1108/30:110; dated October 28, 1977. Unpublished study submitted by Chevron Chemical Co., Richmond, CA.
81-5	00014220	Levy, J.E. (1979). The Skin Irritation Potential of Monitor Technical; Chevron Chemical Co., Richmond, CA; Report No. SOCAL 1445/39:24; dated June 19, 1979. Unpublished study submitted by Chevron Chemical Co., Richmond, CA.
81-6	00147929	Korenaga, G. L., Cushman, J. R. and Wong, Z. A. (1984). Modified Buehler Test for the Skin Sensitization Potential of Methamidophos Technical (SX-1490); Chevron Environmental Health Center, Richmond, CA.; Report Number: SOCAL 2135, dated November 13, 1984. Unpublished study submitted by Chevron Chemical Co., Richmond, CA and Mobay Chemical Co., Kansas City, MO.
81-7	00041317	Kruckenberg, S.M., Fenwick, B.W., Brown, S.M. et al. (1979). Acute Delayed Neurotoxicity Study on Monitor Technical. Kansas State University, Study No. 79ANH01 dated August 29, 1979. Unpublished study submitted by Mobay Chemical Corp., Co., Kansas City, MO.
81-8	43025001	Sheets, L.P. and Hamilton, B.F. (1993). An Acute Oral Neurotoxicity Screening Study with Technical Grade Methamidophos (MONITOR®) in Rats. Miles Inc. Agriculture Division, Stilwell, KA, Report No. 92-412-

QL; dated November 5, 1993. Unpublished study submitted by Miles Inc. Agriculture Division Stilwell, KA.

81-8 43345801 Sheets, L.P. (1994). An Acute Oral Neurotoxicity Screening Study with Technical Grade Methamidophos (MONITOR®) in Rats. Miles Inc., Agricultural Division, Toxicology, Stilwell, KA, Study Nos. 105053-1 and 94-412-YW; dated August 12, 1994. Unpublished study submitted by Miles Inc., Agricultural Division, Kansas City, MO.

82-1a 00014155 Loser, E. (1970). Subchronic Toxicological Studies on Rats: Three-Month Feeding Experiment. Farbenfabriken Bayer, AG, Report Nos. 2165; 28043; received November 18, 1974. Unpublished study submitted by Chevron Chemical Co., Richmond, CA.

82-1b 00014153 Loser, E. (1970). Subchronic Toxicological Studies on Dogs: Three-Month Feeding Experiment. Farbenfabriken Bayer, AG, Report Nos. 2164; 27986; received November 18, 1974. Unpublished study submitted by Chevron Chemical Co., Richmond, CA.

82-1ss 41867201 Christenson, W.R. (1991). Technical Grade Methamidophos (MONITOR): An Eight-Week Subchronic Cholinesterase Study in Fischer 344 Rats. Mobay Corp., Corporate Toxicology Department, Stilwell, KS, Study No. 89-972-CV; dated March 19, 1991. Unpublished study submitted by Mobay Corp., Kansas City, MO.

82-1ss 00015160 Garofalo, M. (1973). A Study of the Effects of Orthene and Monitor on Plasma and Erythrocyte Cholinesterase Activity in Human Subjects During Subacute Oral Administration. Industrial BIO-TEST Laboratories, Inc., Northbrook, IL, Study No. IBT No. 636-02498; dated March 7, 1973. Unpublished study submitted by Chevron Chemical Co., Richmond, CA.

82-2 44525301 Sheets, L.P. and Gastner, M.E. (1997) Repeated-Dose 21-Day Dermal Toxicity Study with Technical Grade Methamidophos (Monitor) in Rats. Bayer Corporation, Agriculture Division, Toxicology. 17745 South Metcalf, Stilwell, Kansas. Study Number 96-122-KQ. December 10, 1997. Unpublished study submitted by Bayer Corp., Kansas City, MO.

Sheets, L.P., Gastner, M.E., and Hamilton, B.F. (1998)Supplemental Report to Repeated-Dose 21-Day Dermal Toxicity Study with Technical Grade Methamidophos (Monitor) in Rats. Bayer Corporation, Agriculture Division, Toxicology. 17745 South Metcalf, Stilwell, Kansas. Addendum to 96-122-KQ. September 28, 1998. Addendum to MRID No. 44525301. Unpublished study submitted by Bayer Corp., Kansas City, MO.

82-4 41402401 Pauluhn, J. and Cole, R.M. (1988). SRA 5172 (Methamidophos): Study of the Subchronic Inhalation Toxicity to Rats in Accordance with OECD Guideline No.

		413 and Addendum to Study of the Subchronic Inhalation Toxicity to Rats in Accordance with OECD Guideline No.413. Bayer AG, Wuppertal, Germany; Report Nos. 98370 and T9022366 (main study); 98370-1 and T9022366 (addendum) study completion date March 30, 1988. Unpublished study submitted by Valent USA Corporation, Walnut Creek, CA.
82-5a	40985202	Sachsse K. (1987). 3-Month Subchronic Delayed Neurotoxicity Study with SRA 5172 (C.N. Methamidophos). KFM Kleintierfarm Madoerin AG, Fuellinsdorf SZ/ RCC Research and Consulting Co. AG, Itingen, SZ/ RCC UMWELTCHEMIE AG, Itingen, SZ Study Nos. 94213/064293; dated November 15, 1987. Unpublished study submitted by Bayer AG, Wuppertal, SZ/Valent (Chevron).
82-7	43197901	Sheets, L.P. and Hamilton, B.F. (1994). A Subchronic Dietary Neurotoxicity Screening Study with Technical Grade Methamidophos (MONITOR®) in Fischer 344 Rats. Miles Inc. Agriculture Division, Stilwell, KS, Report No. 106351/92-472-RE; dated April 13, 1994. Unpublished study submitted by Miles Inc. Agriculture Division Stilwell, KS.
83-1	00147938N	Hayes, R. H. (1984). One-year Feeding Study of Methamidophos (Monitor) in Dogs. Mobay Chemical Corp., Toxicology Dept., Stilwell, KS; Study No. 81-174-01; dated June 26, 1984. Unpublished study submitted by Mobay Chemical Corp., Kansas City, MO/Chevron Chemical Co., Richmond, CA.
	41234304*	Hayes, R. H. (1984). One-year Feeding Study of Methamidophos (Monitor) in Dogs. Mobay Chemical Corp., Toxicology Dept., Stilwell, KS; Study No. 87474-1; Unpublished study submitted by Mobay Chemical Corp., Kansas City, MO
83-2a	00148452N	Hayes, R. H. (1984). Chronic Feeding/Oncogenicity Study of Technical Methamidophos (Monitor) to Rats. Mobay Chemical Corp., Toxicology Dept., Stilwell, KS; Study No. 81-271-01; dated November 13, 1984. Unpublished study submitted by Mobay Chemical Corp., Kansas City, MO/Chevron Chemical Co., Richmond, CA.
	43248102*	Hayes, R. H. (1994). Chronic Feeding/Oncogenicity Study of Technical Methamidophos (Monitor) to Rats (Report Addendum). Miles Agricultural Division Toxicology, Kansas City, MO; Study No. 81-271-01. Unpublished study submitted by Mobay Chemical Corp., Kansas City, MO/Chevron Chemical Co., Richmond, CA.
83-2b	00145579N	Hayes, R. H. (1984). Oncogenicity Study of Methamidophos Technical (Monitor) on Mice. Mobay Chemical Corp., Toxicology Dept., Stilwell, KS; Study No. 80-332-01; dated August 6, 1984. Unpublished study submitted by Mobay Chemical Corp., Kansas City, MO.
	43248101*	Hayes, R. H. (1994). Oncogenicity Study of Methamidophos Technical (Monitor) on Mice: (Report

Addendum). Miles Agricultural Division Toxicology, Kansas City, MO; Study No. 80/332/01. Unpublished study submitted by Mobay Chemical Corp., Kansas City, MO.

83-3a 00148454 Hixson, E. J. (1984). Embryotoxic and Teratogenic Effects of Methamidophos (Monitor) in Rats. Mobay Chemical Corp., Toxicology Dept., Stilwell, KS; Study No. 82-611-01; dated October 15, 1984. Unpublished study submitted by Mobay Chemical Corp., Kansas City, MO/Chevron Chemical Co., Richmond, CA.

83-3a 43906901 Astroff, B. A. (1996). A Developmental Toxicity Study with MONITOR® Technical in the Sprague-Dawley Rat. Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KA; Report No. 107178 and Study No. 95-612-EM; January 17, 1996. Unpublished study submitted by Bayer Corporation, Agriculture Division, Toxicology, Kansas City, MO.

83-3b 00041315 Machemer, L. (1979). SRA 5172 (Methamidophos): Studies of Embryotoxic and Teratogenic Effects on Rabbits Following Oral Administration. Bayer AG, Institute Fur Toxikologie, Wuppertal-Elberfeld, Germany; Study Nos. 8410 (Bayer AG)/67990 (Chemagro); dated May 31, 1979. Unpublished study submitted by Mobay Chemical Corp.(Chemagro), Kansas City, MO.

83-3b 44040601 Hobermam, A.M. (1996). Oral (Stomach Tube) Developmental Toxicity Study of MONITOR® Technical in Rabbitts. Argus Research Laboratories, Inc., Horsham, PA; Report Nos. 222-001 and VP-10143; March 8, 1996. Unpublished study submitted by Valent U.S.A. Corp., Walnut Creek, CA.

83-4 00148455N Hixson, E. J. (1984). Effect of Methamidophos (Monitor) on Reproduction in Rats. Mobay Chemical Co., Stilwell, KS; Study No. 82-671-01; dated November 8, 1984. Unpublished study submitted by Mobay Chemical Corp., Kansas City, MO/Chevron Chemical Co., Richmond, CA.

41234301* Hixson, E. J. (1984). Effect of Methamidophos (Monitor) on Reproduction in Rats. Mobay Chemical Co., Stilwell, KS; Project ID 88686-1. Unpublished study submitted by Mobay Chemical Corp., Kansas City, MO/Chevron Chemical Co., Richmond, CA.

444660001N Eigenberg, D.A. and Freshwater, K.J. (1998) A Two-Generation Dietary Reproduction Study in Rats Using Technical Methamidophos. Bayer Corporation, Agricultural Division, 17745 South Metcalf, Stilwell, KS 66085-9104. Study Number 95-672-GJ. January 5, 1998. Unpublished study submitted by Bayer Corp., Kansas City, MO.

44815401* Astroff, A.B. and Eigenberg, D.A. (1998) Supplemental Submission to a Two-Generation Dietary Reproduction Study in Rats Using Technical Methamidophos. Bayer

Corporation, Agricultural Division, Toxicology, 17745 South Metcalf, Stilwell, KS 66085-91401. Addendum to Study Number 95-672-GJ. October 9, 1998. Unpublished study submitted by Bayer Corp., Kansas City, MO.

44815402* Moore, K.D. (1999) Supplemental Submission to a Two-Generation Reproduction Study in Rats with Technical Grade Methamidophos (MONITOR®). Bayer Corporation, Agricultural Division, Toxicology, 17745 South Metcalf, Stilwell, KS 66085-91401. Addendum to Study Number 95-672-GJ. February 23, 1999. Unpublished study submitted by Bayer Corp., Kansas City, MO.

84-2 00098457 Machado, M.L. (1982). Salmonella/Mammalian Microsome Mutagenicity Test (Ames) with Monitor Technical; Standard Oil of California; Study No. SOCAL 1711; dated February 3, 1982. Unpublished study submitted by Chevron Chemical Co., Richmond, CA.

84-2 42013701 Harbell, J. W. and Jacobson-Kram, D. (1990). CHO/HGPRT Mutation Assay. Microbiological Associates, Inc., Rockville MD; Study No. T5844.332008; dated January 12, 1990. Unpublished study submitted by Mobay Corp., Stilwell, KA.

84-2 42854701 Bigger, C.A.H. and Sigler, C.I. (1993). CHO/HGPRT Mutation Assay -- Monitor Technical. Microbiological Associates, Inc., Rockville MD; Study Nos. TC865.332 (Testing Facility); 930C500-SO (Sponsor) 82-671-01; dated May 27, 1993. Unpublished study submitted by Miles Inc., Kansas City, MO.

84-2 41461401 Murli, H. (1990). Mutagenicity Test on SRA 5172 in an In Vitro Cytogenetic Assay Measuring Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells. Hazleton Laboratories America, Inc., Vienna. VA; Study No. 100024/HLA 10972-0-437; dated January 19, 1990. Unpublished study submitted by Bayer AG/Mobay Corp.

84-2 41234306 Esber, H.J. (1983). In Vivo Cytogenetic Study in Mice. Methamidophos Technical (SX-1244). EG & G Mason Research Institute, Worcester, MA; Study No. MRI-176-CCC-82-56; dated November 18, 1983. Unpublished study submitted by Valent USA Corp./Chevron Chemical Co.

84-2 41234305 Curren, R.D. (1988). Unscheduled DNA Synthesis in Rat Hepatocytes. Microbiological Associates, Inc., Rockville MD; Study Nos. T5844.380 (Testing Facility); 99172 (Sponsor); dated October 24, 1988. Unpublished study submitted by Mobay Corp., Stilwell, KS.

85-1 00015224 Crossley, J.and Tutass, H.D. (1969). Metabolism of Monitor Insecticide by Rats. Received March 27, 1973 under 239-EX-60. Unpublished study submitted by Chevron Chemical Co., Richmond, CA.

41685801 Johnson, M.K. and Lotti, M. (1989). Can Methamidophos Cause Delayed Polyneuropathy in Man or Test Animals? -- Review Article. Medical Research Council Toxicology

Unit, Surrey, United Kingdom and Universita degli Studi di Padova, Instituto di Medicina del Lavoro, Padova, Italy; Report Number 100277; Report Issued November 1989. Review Article submitted by Mobay Corp., Kansas City, MO.

41685803 Flucke, W. (1990). Methamidophos (Tamaron) (Racemate and Enantiomers): Study for Acute Oral Toxicity to the Hen (Gallus domesticus); Bayer AG, Wuppertal, Germany; Report No. 100279; Report Issued May 29, 1990. Unpublished study submitted by Mobay Corp., Kansas City, MO.

41685804 Flucke, W. and Eben, A. (1990). Methamidophos (Racemate and Enantiomers): Study for Effect on NTE (Neuropathy Target Esterase) in Hens Following Oral Administration; Bayer AG, Wuppertal, Germany; Report No. 100280; Report Issued May 29, 1990. Unpublished study submitted by Mobay Corp., Kansas City, MO.

41685805 Flucke, W. (1990). Methamidophos (Racemate and Enantiomers) Study for OPIDP (Organophosphorus Ester-Induced Delayed Polyneuropathy): Exploratory Studies on Hens; Bayer AG, Wuppertal, Germany; Report No. 100281; Report Issued April 10, 1990. Unpublished study submitted by Mobay Corp., Kansas City, MO.

N Main Study
* Additional Study Information

Additional References:

Lotti, M., Moretto, A., Bertolazzi, M., Peraica, M, and Fioroni, F. (1995). Organophosphate polyneuropathy and neuropathy target esterase: studies with methamidophos and its resolved optical isomers. Arch. Toxicol. 69(5) p 330-336.

McConnell, R., Keifer, M., and Rosenstock, L. (1994). Elevated quantitative vibrotactile threshold among workers previously poisoned with methamidophos and other organophosphate pesticides. Am. J. Ind. Med. 25(3) p 325-34.

Senanayake, N. and Johnson, M.K. (1982). Acute polyneuropathy after poisoning by a new organophosphate insecticide. Medical Intelligence 306(3) p 155-157.

Zheng, R.Y. (1990). Clinical features of delayed polyneuropathy induced by acute methamidophos toxicosis in 74 cases. Chung-Hua-Nei-Ko-Tsa-Chin 29(2) p 79-82.

SignOff Date:	7/1/99
DP Barcode:	D256737
HED DOC Number:	256737
Toxicology Branch:	TOX1